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14. ABSTRACT
The PIs constructed a novel network modeling framework that is uniquely suited to investigating the neuronal regulation of sleep and wake states. Using this novel framework, the PIs have modeled interactions among primary brainstem and hypothalamic nuclei involved in sleep-wake regulation. The model network exhibits realistic sleep-wake behavior consisting of wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep states. Using this mathematical modeling framework, the PIs conducted modeling studies on several fronts investigating circadian and homeostatic regulation of sleep-wake behavior. Results have contributed to scientific progress in the experimental manipulation of neurotransmitter environments in specific neuronal populations through targeted microinjection of neurotransmitter agonists and antagonists; the feed-forward and feedback synaptic interactions between the SCN and sleep-wake nuclei that provide circadian modulation of sleep-wake behavior; the hypothesis that sleep-wake regulatory mechanisms are preserved across mammalian species; and the competing proposed network structures for the regulation of REM sleep.

15. SUBJECT TERMS

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Final Report on Activities
January 1, 2008 – July 31, 2011

Project Title: Mathematical Modeling of Circadian and Homeostatic Interaction
Institution: University of Michigan
PI: Victoria Booth
Co-PIs: Daniel Forger and Cecilia Diniz Behn
Project Period: 01/01/2008 – 01/31/2011, extended to 07/31/2011

Summary of Progress

During the grant period, the PIs have constructed a novel network modeling framework that is uniquely suited to investigating the neuronal regulation of sleep and wake states. The framework describes both neuronal activity in populations of neurons and concentrations of the neurotransmitters released by these nuclei. A firing-rate formalism is implemented to model neuronal activity levels and population-level neurotransmitter release is governed by firing rates in associated pre-synaptic populations. Distinct neuronal populations are coupled through neurotransmitter action according to established excitatory/inhibitory effects on post-synaptic targets. Using this novel framework, the PIs have modeled interactions among primary brainstem and hypothalamic nuclei involved in sleep-wake regulation. The model network exhibits realistic polyphasic sleep-wake behavior consisting of wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep states. In addition, the model captures stereotypical sleep patterning including cycling between NREM and REM sleep.

Using this mathematical modeling framework for neuronal population firing rate and neurotransmitter expression, the PIs conducted modeling studies on several fronts investigating circadian and homeostatic regulation of sleep-wake behavior.

In the network model, they have simulated experimental studies that manipulate the neurotransmitter environments in specific neuronal populations through targeted microinjection of neurotransmitter agonists and antagonists. Simulations of specific microinjection experiments that probed the role of a key wake-promoting population in REM sleep regulation indicated limitations of the specific network structure as well as of current models of certain physiological processes in accounting for all observations.

The PIs constructed a combined network model of the brainstem and hypothalamic sleep-wake regulatory populations coupled with a firing rate model of the suprachiasmatic nucleus (SCN). Physiologically determined, feedforward and feedback synaptic interactions between the SCN and sleep-wake nuclei provided circadian modulation to the sleep-wake regulation populations. They investigated several physiological mechanisms which could account for circadian modulation of sleep-wake activity by SCN synaptic activity and also for sleep-wake patterning that occurs when the SCN is lesioned. Interestingly, accounting for patterning in both the intact and lesioned SCN conditions in the model required both sleep-promoting and wake-promoting signaling from the SCN, a result that has been hypothesized by the experimental community but had previously not been included in sleep-wake regulation models in a physiologically-realistic manner.

Using their model of the brainstem and hypothalamic sleep-wake regulatory network, the PIs investigated the hypothesis that regulatory mechanisms are preserved across mammalian species.

They determined necessary differences in model components and parameters to generate sleep-wake patterning in rat and mouse across the light-dark cycle, and in rat and cat during the rest phase. The particular novelty of this study was attention paid to fitting model dynamics to higher-order statistics of sleep-wake patterning, including the distribution profiles of wake, NREM and REM sleep bout durations. The PIs propose that accounting for the fine temporal architecture of sleep-wake patterning in mammals showing polyphasic behavior can be a source of significant constraining information for mechanistic models of the sleep-wake regulatory network. Analysis of model results suggested specific physiological differences between species that can be experimentally tested.

The PIs investigated competing proposed network structures for the regulation of REM sleep and the conditions required in the competing proposed structures to generate cycling of REM sleep as observed robustly in human sleep patterns. They used a reduced model formalism that allowed rigorous analysis of the existence of periodic solutions, and dependence of stable periodic solutions on network components. These results provide specific restrictions on the generation of time-varying dynamics inherent to each of the proposed competing structures that cannot be determined by current experimental techniques.

Peer-reviewed Journal Publications

1) Diniz Behn, C. and Booth, V. Simulating microinjection experiments in a novel model of the rat sleep-wake regulatory network. *J Neurophysiol*, 103: 1937-1953, 2010.

2) Fleshner, M., Booth, V., Forger, D. and Diniz Behn, C. Multiple signals from the suprachiasmatic nucleus are required for circadian regulation of sleep-wake behavior in the nocturnal rat. *Phil Trans R Soc A*, 369:3855-3883, 2011.

3) Diniz Behn, C. and Booth, V. Modeling the temporal architecture of rat sleep-wake behavior. *Conf Proc IEEE Eng Med Biol Soc* 2011:4713-4716, 2011 (peer-reviewed conference paper).

4) Walsh, C.M., Booth, V. and Poe, G.R. Spatial and reversal learning in the Morris water maze are largely resistant to 6 hrs of REM sleep deprivation following training. *Learn & Mem*, 18(7):422-34, 2011.

5) Williams, K. and Diniz Behn, C. Investigating the role of dynamics in a model orexin neuron's response to orexin and dynorphin. *J Biol Rhythms*, 26:171-181, 2011..

6) Diniz Behn, C. and Booth, V. Fast-slow analysis of REM sleep dynamics. *SIAM J Appl Dyn Sys*, in revision, 2011.

Book Chapters

1) Poe, G.R., Booth, V., Bjorness, T.E., Riley, B.T. and Watts, A.C. Sleep is for unfinished business: Growing evidence that sleep is important for learning and memory. In: Current Advances in Sleep Biology, M.G. Frank, ed. Nova Publishers, 2009.

2) Diniz Behn, C. and Booth, V. A population network model of neuronal and neurotransmitter interactions regulating sleep-wake behavior in rodent species. In: Sleep and anesthesia: Neural correlates in theory and experiment, A. Hutt, ed. Springer, 2011.
3) Diniz Behn, C. Mathematical models of narcolepsy. In: Narcolepsy: Pathophysiology, Diagnosis, and Treatment, C. Baumann, T. Scammell, and C. Bassetti, eds. Springer, 2011.
4) Pal, D., Booth, V. and Poe, G.R. Sleep-related hippocampal activation: Implications for spatial memory consolidation. In: Rapid Eye Movement Sleep: Regulation and Function, B.N. Mallick, S.R. Pandi-Perumal, R. McCarley and A. Morrison, eds. Cambridge University Press, 2011.

Manuscripts in preparation

- C. Diniz Behn, D. Pal, G. Vanini, R. Lydic, G. A. Mashour and V. Booth. Modeling temporal architecture of sleep-wake patterning in multiple mammalian species.
- Diniz Behn, C., Ananthasubramanian, A., and Booth, V. Cycling in REM sleep regulatory networks.

Published Abstracts

1) C. Diniz Behn and V. Booth. Simulating microinjection of GABA agonists and antagonists in a novel model of the sleep-wake regulatory network. 38th Annual Meeting of the Society for Neuroscience, 586.22, 2008.
2) C. Diniz Behn and V. Booth. Modeling the interaction between circadian and sleep-wake regulatory systems. 39th Annual Meeting of the Society for Neuroscience, 376.29, 2009.
3) K. Williams and C. Diniz Behn. A Hodgkin-Huxley-type model orexin neuron. SLEEP 32, A25, 2009.
4) C. Diniz Behn, D. Pal, G. Vanini, R. Lydic, G. A. Mashour and V. Booth. Modeling sleep-wake temporal architecture in multiple species to investigate underlying physiology of behavioral state regulation. 40th Annual Meeting of the Society for Neuroscience, 300.18, 2010.
5) C. Diniz Behn. Insights from mathematical modeling of sleep/wake behavior. Sleep and Biol Rhyth 9, 221, 2011.
6) C. Diniz Behn, D. Pal and V. Booth. Modeling the fine temporal architecture of rat sleep-wake behavior. 41st Annual Meeting of the Society for Neuroscience, 721.05, 2011.

Grant-related Educational Activities

1) V. Booth and C. Diniz Behn mentored the following University of Michigan undergraduate students in research projects that contributed to the grant aims:

- Katherine Williams, 2008-2009. Currently, Katie is a PhD student in the Department of Mathematics at the University of Arizona.
- Michelle Fleshner, 2009-2010. Michelle will be starting at Tulane University Medical School in Fall 2012.
- Aparna Ananthasubramanian, Summer 2010. Aparna is currently completing her undergraduate degree at Stanford University.
- Rebecca Gleit, Summer 2011 – current. Rebecca is currently in her junior year at the University of Michigan.

2) V. Booth contributed lectures discussing modeling of sleep-wake regulation to the University of Michigan course Psych 533/ Neurosci 520: Sleep: Sleep, Neurobiology and Medicine in Fall 2010 and 2011.
3) C. Diniz Behn developed a course module pertaining to mathematical modeling of sleep and circadian rhythms for University of Michigan course Math 463: Mathematical Modeling in Biology in Fall 2010.

Presentations

1) Booth, V., "A novel population model for NREM/REM sleep regulation", invited presentation, Dynamical Systems in Biology workshop, New York University, New York, April 2008.
2) Booth, V., "A novel population model for NREM/REM sleep regulation", invited presentation, Mathematical Biology seminar, New Jersey Institute of Technology, Newark, April 2008.
3) Booth, V., "A novel population model for sleep-wake regulation", invited presentation, Biological Physics Seminar, University of Michigan, Ann Arbor, November 2008.
4) Diniz Behn, C., "A novel population model for NREM/REM sleep regulation", minisymposium presentation, SIAM Conference on the Life Sciences, Montreal, August 2008.
5) C. Diniz Behn and V. Booth, "Simulating microinjection of GABA agonists and antagonists in a novel model of the sleep-wake regulatory network", poster presentation, 38th Annual Meeting of the Society for Neuroscience, Washington DC, 2008.
6) V. Booth, "Simulating microinjection of neurotransmitter agonists and antagonists in a novel model of the sleep-wake regulatory network", FACM 09, 6th Annual Conference on Frontiers in Applied and Computational Mathematics Conference, New Jersey Institute of Technology, June 2009.
7) V. Booth, "Dynamics of a novel model of the sleep-wake regulatory network: A fast-slow analysis", Conference on Neural Dynamics and Computation, held in honor of John Rinzel, New York University, June 2009.
8) V. Booth, "A novel population model for sleep-wake regulation", Workshop on "Anaesthesia and sleep: recent experimental and theoretical aspects" at CNS*09, 18th Annual Computational Neuroscience Meeting, Berlin, July 2009.

9) C. Diniz Behn, "A neurotransmitter-driven approach to modeling sleep-wake regulation", Biological rhythms seminar, University of Michigan, January 2009.

10) C. Diniz Behn, "Mathematical models of narcolepsy", invited presentation, International symposium on narcolepsy, Ascona, Switzerland, September 2009.

11) K. Williams, "A Hodgkin-Huxley-type model orexin neuron", Associated Professional Sleep Societies Annual Meeting, Seattle, WA, June 2009.

12) K. Williams, "Dynamics in a Hodgkin-Huxley-type model orexin neuron", Society for Industrial and Applied Mathematics Annual Meeting, Denver, CO, July 2009.

13) M. Fleshner, C. Diniz Behn and V. Booth. Modeling the interaction between circadian and sleep-wake regulatory systems. 39th Annual Meeting of the Society for Neuroscience, Chicago, October 2009.

14) M. Fleshner, C. Diniz Behn and V. Booth. Modeling the interaction between circadian and sleep-wake regulatory systems, Systems Biology Symposium, University of Michigan, December 2009.

15) C. Diniz Behn, Networks, nullclines, and narcolepsy: a mathematical investigation of orexin neurons, invited presentation, The Ohio State University, Columbus, OH, February 2010.

16) C. Diniz Behn, Investigating the dynamics of REM sleep, invited presentation, University of Utah, Salt Lake City, UT, February 2010.

17) V. Booth, Modeling neuronal interactions between circadian and sleep-wake regulatory systems, Biological Rhythms and Sleep seminar, University of Michigan, Ann Arbor, March 2010.

18) C. Diniz Behn, Modeling the interaction between circadian and sleep/wake regulatory systems, Frontiers in Applied and Computational Mathematics, New Jersey Institute of Technology, Rutgers, NJ, May 2010.

19) C. Diniz Behn, Modeling the neuronal interaction between the SCN and sleep-wake regulatory systems, SIAM Life Sciences Meeting, July 2010.

20) C. Diniz Behn, Investigating the role of dynamics in a model orexin neuron's response to orexin and dynorphin, SIAM Annual Meeting, July 2010.

21) V. Booth, Modeling the neuronal interactions between circadian and sleep-wake regulatory systems, Annual University of Michigan – Michigan State University Circadian Clocks Meeting, August 2010.

22) V. Booth, Modeling of the neuronal sleep-wake regulatory network, Biopsychology seminar, University of Michigan, Ann Arbor, October 2010.

23) C. Diniz Behn, D. Pal, G. Vanini, R. Lydic, G. A. Mashour and V. Booth. Modeling sleep-wake temporal architecture in multiple species to investigate underlying physiology of behavioral state regulation. 40th Annual Meeting of the Society for Neuroscience, San Diego, November 2010.

24) C. Diniz Behn, Time to sleep: modeling interactions between circadian and sleep/wake regulatory systems, invited presentation, Hampshire College, Amherst, MA, December 2010.

25) C. Diniz Behn, Mathematics of dreaming: the dynamics of REM sleep, Math Biology Forum, University of Michigan, Ann Arbor, December 2010.

26) C. Diniz Behn, Mathematical modeling of REM sleep regulation, invited presentation, University of California, Davis, CA, January 2011.

27) C. Diniz Behn, Modeling the fine temporal architecture of rat sleep-wake behavior, poster presentation, Current Trends Workshop: New Developments in Dynamical Systems Arising from the Biosciences, Mathematical Biosciences Institute, The Ohio State University, March 2011.

28) C. Diniz Behn, Modeling the fine temporal architecture of rat sleep-wake behavior, poster presentation, Systems Biology Symposium, University of Michigan, April 2011.

29)

30) C. Diniz Behn, Developing multi-scale models of sleep/wake regulation, invited presentation, Radcliffe Institute Workshop, Harvard University, Cambridge, MA, March 2011.

31) V. Booth, Overview of sleep-wake regulation and dynamics, opening speaker and organizer of minisymposium on Modeling Dynamics of Sleep-Wake Regulation at the SIAM Conference on Applications of Dynamical Systems, Snowbird, Utah, May 2011.

32) C. Diniz Behn, Modeling circadian modulation of sleep-wake regulatory dynamics, organizer of minisymposium on Modeling Dynamics of Sleep-Wake Regulation at the SIAM Conference on Applications of Dynamical Systems, Snowbird, Utah, May 2011.

33) V. Booth, Modeling the temporal architecture of rat sleep-wake behavior, International Conference of the IEEE Engineering in Medicine and Biology Society, Boston, September 2011.

Symposia Organized

1) "Investigating Neural Mechanisms of Sleep and Anesthesia through Modeling" at the SIAM Life Sciences Conference, Montreal, July 2008. Organizer: C. Diniz Behn. Speakers and presentation titles were:

    - A Novel Neural Population Model for Investigating NREM/REM Sleep Regulation. Cecilia Diniz Behn and Victoria Booth, University of Michigan.
    - A Quantitative, Metabolic Theory for Mammalian Sleep. Van Savage, Harvard Medical School.
    - A Mathematical Model of the Sleep/Wake Cycle Based on Neurophysiology. Michael Rempe, Janet Best, and David H. Terman, The Ohio State University.
    - A Computational Study of the Network Mechanisms Mediating Anesthesia-Induced Paradoxical Excitation. Michelle McCarthy, Boston University; Emery Brown, Harvard Medical School, Massachusetts General Hospital and Massachusetts Institute of Technology; Nancy J. Kopell, Boston University

- Clustering, Multistability, and the Complex Neuronal Coding of Daily Timekeeping. Daniel Forger and Casey Diekman, University of Michigan.

2) University of Michigan-Ohio State University Sleep Modeling Research Symposium on September 18, 2008 at the University of Michigan. Organizers: V. Booth, C. Diniz Behn and D. Forger. Participants and speakers included:, Janet Best (OSU), Victoria Booth (UM), Casey Diekman (UM), Cecilia Diniz Behn (UM), Danny Forger (UM), Badal Joshi (OSU), Michael Rempke (OSU), David Terman (OSU).

3) "Multi-Scale Modeling of Mammalian Circadian Clocks" at the SIAM Life Sciences Conference, Pittsburgh, July, 2010. Organizers: C. Diniz Behn and R. Yamada. Speakers and presentation titles were:

    - Modeling the Precision of Circadian Oscillators, Felix Naef, Ecole Polytechnique Federale de Lausanne
    - Bioluminescence Recordings to Entrainment Properties: Quantifying the Circadian Clock, Pal Westermark, Humboldt University
    - Modeling the Circadian Clock: From Molecular Mechanism to Physiological Disorders, Jean-Christophe Leloup, Universite Libre de Bruxelles
    - Modeling the Electrophysiology of the Suprachiasmatic Nucleus, Casey Diekman, University of Michigan
    - Modeling the Neuronal Interaction Between the SCN and Sleep-wake Regulatory Systems, Cecilia Diniz Behn, University of Michigan
    - Using Physiologically-based Modeling to Determine the Mechanisms Underlying Complex Sleep/wake Dynamics, Andrew Phillips, Brigham and Women's Hospital and Harvard Medical School
    - Dynamics of Sleep/wake Homeostatic Degradation and Circadian Modulation of Cognitive Performance, Pete McCauley, Washington State University
    - Mathematical Modeling of Human Circadian Rhythms and Performance, Elizabeth Klerman, Brigham and Women's Hospital and Harvard Medical School

4) "Modeling Dynamics of Sleep-Wake Regulation" at the SIAM Conference on Applications of Dynamical Systems, Snowbird, May, 2011. Organizers: V. Booth, A. Bose, C. Diniz Behn and B. Gluckman. Speakers and presentation titles were:

    - Overview of Sleep-Wake Regulation and Dynamics, Victoria Booth, University of Michigan
    - Ultradian Dynamics in a Potential Formulation of Human Sleep, Andrew Phillips, Brigham and Women's Hospital and Harvard Medical School; Peter Robinson, University of Sydney; Elizabeth Klerman, Brigham and Women's Hospital and Harvard Medical School.
    - Mechanisms for controlling REM sleep patterns, Amitabha Bose, New Jersey Institute of Technology

- Modeling the Human Sleep-Wake Cycle, Michael Rempe, Whitworth University; Janet Best and David H. Terman, The Ohio State University
- Modeling circadian modulation of sleep-wake regulatory dynamics, Cecilia Diniz Behn, Michelle Fleshner, Daniel Forger, and Victoria Booth, University of Michigan
- High-resolution sleep scoring through the mapping of EEG onto a cortical state model, Beth A. Lopour, University of California, Los Angele; Savas Tasoglu, University of California, Berkeley; Heidi E. Kirsch, University of California, San Francisco; James W. Sleigh, University of Auckland, New Zealand; Andrew J. Szeri, University of California, Berkeley
- Data Assimilation in Sleep Models - a Nonlinear Ensemble Kalman Approach To Tracking and Predicting State, Madineh Sedigh-Sarvestani, Steven Schiff, and Bruce J. Gluckman, Pennsylvania State University